AMENDMENTS

In the claims

Please amend claim 12 as follows:

12. (Twice Amended) A method of inducing sustained immunological tolerance in an individual to an allergen or a mucosal antigen, comprising administering to a mucosal surface of the individual a composition comprising an effective amount of a mucosal binding component selected from the group consisting of a cholera toxin B peptide (CTB) or an *E. coli* heat-labile enterotoxin B subunit (LTB) peptide in an unconjugated form.

REMARKS

The present Amendment is in response to the Examiner's Office Action mailed May 9, 2000. Claims 1-3 and 5-20 are pending in this application, with claims 21-26 withdrawn from consideration by the Examiner under 37 C.F.R. §1.142(b) as being drawn to a non-elected invention. Applicants express their appreciation for the withdrawal of the rejections of (now cancelled) claim 4 under 35 U.S.C., §§112, 1st and 2nd paragraphs and 103(a) and of claim 6 under 35 U.S.C., 2nd paragraph. By this Amendment, claim 12 has been amended.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

I. Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 2 and 5-20 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner contends that the Specification does not provide guidance in the art for substituting unconjugated *E. coli* heat-labile enterotoxin B subunit peptide (LTB) for cholera

toxin B peptide (CTB) because the history of the art only supports LTB linked to tolerogens. Applicants respectfully traverse the Examiner's position.

Applicants contend that it has been known in the art that among mucosal binding proteins, LTB especially binds to the same receptor in the gut as CTB, namely ganglioside GM1, with an affinity that is comparable to the affinity of CTB for this receptor. In support of this proposition, Applicants attach a publication by Backstrom, M. et al., Structural basis for differential receptor binding of cholera and *Escherichia coli* heat-labile toxins: influence of heterologous amino acid substitutions in the cholera B-subunit, Molecular Microbiology, 24(3), pp. 489-497 (1997).

Furthermore, the Specification describes mucosal binding proteins binding to the GM1 receptor to be especially preferred (*see* page 15, lines 21-26. "Preferred mucosal binding components of this invention are capable of binding gangliosides expressed in the mucosa, preferably the ganglioside GM1"). It is also specified that "a molecule . . . having ganglioside or GM1 binding activity require no other property to meet the definition of a mucosal binding component." (Specification. page 15, lines 25-26). As it is well known in the art that LTB also possesses the critical "GM1 binding activity" of CTB, a person skilled in the art would find guidance in the present invention to substitute unconjugated LTB for CTB in view of the history in the art.

Furthermore, the inventor Mr. Jacob Sten Petersen, in an attached declaration under 37 C.F.R. §1.132, provides experimental data demonstrating that the GM1 binding activity of CTB is responsible for the stronger induction of oral tolerance against a given antigen when this antigen is administered in combination with CTB in an unconjugated form, as described in the Specification. When the GM1 binding activity of CTB in a mixture with an antigen, in this case insulin, is blocked by pre-incubating CTB with GM1, the induction of oral tolerance is severely reduced. Since LTB also possesses this GM1 binding activity, a person skilled in the art would find guidance in the present invention to substitute unconjugated LTB for CTB in view of information known in the art.

In view of the above information and arguments, Applicants respectfully request that the rejection of claims 1, 2 and 5-20 under 35 U.S.C. §112, first paragraph, be withdrawn.

II. Rejection under 35 U.S.C. §103(a)

Claims 1-2 and 5-20 stand rejected under 35 U.S.C. §103(a) for obviousness over JP3109328 in view of Elson (Curr. Topics in Microbiol. 146, 29-33 (1989)). Applicants respectfully traverse the Examiner's position.

Elson addresses CT/CTB as an mucosal adjuvant and specifies that "CT feeding **does not induce oral tolerance**" (page 30, line 4) and "[t]he timing and route of antigen administration is important in this adjuvant property of CT in that adjuvanticity only occurs when both CT and the antigen are given by the same route and at the same time." page 30, line 23. In page 30, line 32, Elson further specifies that "[t]he relative importance of the two subunits in the immunogenicity of CT is not clear. The B subunit (CTB) shares many of the properties of the holotoxin, including the ability to induce secretory IgA responses and the **lack of induction of oral tolerance** after feeding." CTB and CT share many similarities one of which is described in the Elson reference as the ability to **prevent** oral tolerance. Elson describes that CTB **prevents** induction of oral tolerance and does not teach or suggest "sustained immunological tolerance" by CTB as specified in independent claims 1, 12, 15, 19 and 20. Thus Elson **teaches away** from the claims of the present invention which specify a "method of inducing sustained immunological tolerance."

In order to form a proper combination of Elson with JP3109328 it must be demonstrated that the prior art teaches or suggests modifying the prior art in order to render a claimed invention obvious. *In re Dembiczak,* 175 F.3d 994 (1999). In other words, one must be motivated by the prior art to make the necessary modification. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Absent such motivation, a rejection based on a combination of references is unsupported and any rejection based on such a combination must be withdrawn.

The abstract of JP3109328 specifies a transplantation of bone marrow cells **after** the administration of CTB. Elson does not teach or suggest potentiation of oral tolerance and it is not obvious from Elson to administer CTB and bone marrow by the mucosal route. In addition, Elson discloses that it is very important that the antigen (i.e., bone marrow cells) are given **by the same route** and even **at the same time** as CT or CTB.

Furthermore, if bone marrow cells were to be administered by the oral route they would be degraded immediately in the stomach or gut and there will be no graft survival for more than a few seconds. This would clearly frustrate the purpose of the method specified in the abstract of JP3109328. Thus, one of skill in the art would find no motivation to combine Elson with JP3109328 to arrive at the present invention. On the contrary, the references teach away from making such a combination because the method of JP3109328 is inoperable if combined with Elson.

Since Elson teaches away from the claimed invention and there is no motivation to combine Elson and JP3109328 especially since JP3109328 is inoperable in combination with Elson, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103(a), be withdrawn.

III. Rejection under 35 U.S.C. §102(e)

Claims 12, 13 and 14 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Pat. No. 5,681,571 to Holmgren et al. In response Applicants amend claim 12 to specify "a mucosal binding component in an unconjugated form." In view of this amendment, Applicants respectfully traverse the Examiner's position.

Independent claim 12, as amended, cites a limitation concerning the relationship of the mucosal binding component and the antigen, namely that they be in an "**unconjugated form.**" Holmgren et al. teaches that the mucosal binding molecule shall be **linked to** the mucosal antigen for use in the disclosed method of inducing immunological tolerance to a mucosal antigen as specified in the claims as well as in the specification. (Holmgren et al., col. 11, lines

47-59 and in the examples, for instance Example 1, col. 13, lines 18-21, lines 39-40, and lines 56-58). Furthermore, Holmgren et al. have elsewhere published that they did not find any affect on oral tolerance induction by use of a mixture of CTB and antigen in an unconjugated form (*see* Table 2 in Sun et al., Proc. Natl. Acad. Sci., USA 93, 7196-7201 (1996)). This document was cited in the International Search Report and the IDS and is enclosed for the Examiner's convenience.

Therefore, Applicants submit that since Holmgren et al. to not teach or suggest an "unconjugated" mucosal binding component for binding to a mucosal surface to induce sustained immunological tolerance as specified in amended, independent claim 12, it does not anticipate claim 12. Since claims 13 and 14 depend from independent claim 12, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

In light of the arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent and respectfully request the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 273802002200. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: November 9, 2000 By: _____

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